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### Five theories of the mechanism of depression

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# Five theories of the mechanism of depression

Prof. Dr. Anton J.M. Loonen

Dear audience,

The neurobiology of mood disorders has been already for decades the subject of intensive experimental and clinical research. Several theories have been developed to explain the genesis of these disorders. We believe that the different mechanisms implicated by these theories are not independent from one another. Therefore, we will try to describe, how these different theories are interrelated. This will bring us finally to a model how two different brain structures induce low mood. We believe that a dysfunctioning of two different cortical-subcortical circuits is involved in major depressive disorders. The five theories of mood disorders give the mechanisms of how these circuits are affected by genetic and environmental circumstances.



## Pathophysiology of depression

- › Amine hypothesis
- › Biorhythm hypothesis
- › Neuro-endocrine hypothesis
- › Neuro-immune hypothesis
- › Kindling hypothesis

This slides shows the five theories that have been developed to explain the mechanism of major depressive disorder. The first one, the monoamine hypothesis is the oldest one and the neuro-immune hypothesis the youngest. The kindling hypothesis is usually applied to explain recurrent mood swings which occur in bipolar disorders. It does, however, also elucidate the mechanism of a very powerful treatment of both low and elated mood, termed electroconvulsive therapy or ECT.



## Depression may originate from two different brain structures

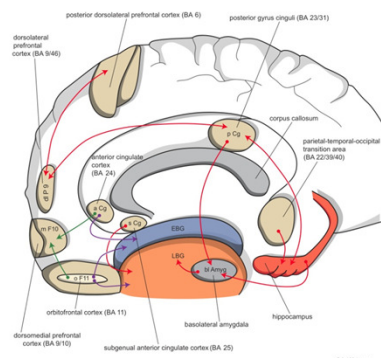
- › ***Brainstem/hypothalamus/basal ganglia***
  - Depression as a '*lust*' disorder
  - Anhedonia and loss of energy
- › ***Hippocampus/amygdala/limbic ganglia***
  - Depression as a '*concern*' disorder
  - Dysphoria and hopelessness

At the end of this lecture we hope to have presented you with evidence, making it possible to propose the existence of two different, although largely overlapping, components of depression. The first component is characterized by the inability to experience pleasure and a loss of energy. The second one is accompanied by feelings of misery and negative expectations for the future. We think that this last type of depression finds its mechanism in a dysfunction of structures within the temporal lobe, while the first one finds its background in a dysfunction of the brainstem, hypothalamus and extrapyramidal basal ganglia.





## Dysfunction of two parallel subcortical circuits may induce depression



### > Extrapyramidal circuit

Cortex → striatum → thalamus → cortex

Striatum: caudate, putamen,  $Acb_C$

### > Limbic circuit

Cortex → ganglia → hypothalamus →  
thalamus → cortex

Ganglia:  $NAcb_s$ , Bed nucleus of the Stria terminalis, extended and central medial amygdala

These two types of depressive symptoms are regulated by two cortical-subcortical-cortical circuits.

The so-called extrapyramidal circuit runs from all neocortical parts of the cerebral cortex through the extrapyramidal basal ganglia to new parts of the thalamus and then back to the frontal cortex. This circuit regulates movement and motivation.

The limbic circuit starts in the limbic cerebral cortex, runs through the limbic basal ganglia to older parts of the thalamus and back to the limbic frontal cerebral cortex. This circuit regulates reactions to escape from trouble.



# Pathophysiology of depression

## > Amine hypothesis

We will start with the mono-amine hypothesis of depression, which is, as we have said, the oldest of them all. In the 1960s Schildkraut developed the idea that a dysfunction of the adrenergic system caused depressive mood disorders and in the 1970s Herman van Praag added his idea that a malfunctioning of serotonergic neurotransmission was to blame for the pathological low mood in depression.



## Amine hypothesis

- › Amine depletion causes depression (reserpine)
- › Antidepressants modify amine transmitters
- › Depression influences amine levels (and metabolites)
  - 5-HIAA levels decrease in CSF
- › Antidepressants change receptor levels
  - 5-HT<sub>1A</sub> receptor decrease in hippocampus
  - $\beta$ -adrenoceptors increase in cerebral cortex

Two observations are at the basis of this theory. Firstly, reserpine, an antihypertensive and antipsychotic drug, which is known to cause a depletion of mono-amine neurotransmitters within the brain, causes a severe major depression in a significant number of the patients who use this drug. Secondly, all known antidepressant drugs at that time were modifying the cerebral levels of the neurotransmitters norepinephrine and serotonin. Tricyclic antidepressants inhibit the reuptake of these transmitters from the synaptic cleft and monoamine oxidase inhibitors or MAO inhibitors diminish their catabolism. Later it was found that the CSF levels of monoamines and their metabolites of depressed patients showed important deviations from non-depressed humans.

Nevertheless, this theory has also important limitations. The effects of antidepressant drugs on monoamine levels occur acutely. However, the therapeutic effects of these drugs show a lag time of about two weeks. After the development of the receptor binding technique in the second half of the 1970s, the existence of this lag time was explained by suggesting that the increased neurotransmitter levels induced a slowly occurring adaptation of their receptors. It was found that chronic treatment with antidepressants induces a decrease of the sensitivity of 5-HT<sub>1A</sub> receptors in the hippocampus and an increase of beta-receptors in the cerebral cortex.



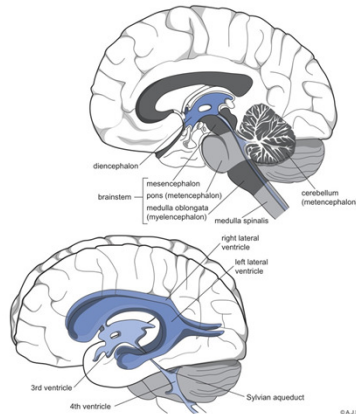
## Amine hypothesis

- › Depression is caused by neurotransmitter dysfunction
  - Hypofunction of adrenergic system
    - Lack of drive
  - Hypofunction of serotonergic system
    - Lack of appropriate mood
  - Hypofunction of dopamine
    - Lack of energy

The essential idea presented in the monoamine hypothesis is that various symptoms of depressive disorder are due to a dysfunctioning of three neurotransmitter systems. It says that the lack of drive is due to a hypofunction of the adrenergic system using norepinephrine as a neurotransmitter. The low mood is due to a hypofunction of the serotonergic system, using 5-hydroxytryptamine or 5-HT. The lack of energy is explained by a hypofunction of the dopaminergic system. This last system is however only directly influenced by nonselective MAO inhibitors and a few other antidepressant drugs.

In order to explain these hypothesis we should depict the basic mechanics of the mind.

## Dysfunctioning of neurotransmitter systems



- › Major systems
  - Glutamate
  - Acetylcholine
  - GABA
- › Minor systems
  - Acetylcholine
  - **Norepinephrine**
  - **Serotonin**
  - **Dopamine**
  - Histamine
- › Special systems
  - NO and CO
  - Neuropeptides
  - Cannabinoids

Neurocommunication largely depends on the usage of chemical substances: neurotransmitters or neurohormones. Only about 5% of the synapses are electrical in nature. The major systems are primarily involved in analysing input and generating output. More interesting, for psychopharmacology at least, were the minor systems. These minor systems regulate the activity level of the major systems. Interfering with their functioning is less detrimental to the functioning of the brain than intervening with for example glutamatergic transmission. Hence, such substances have less toxic effects. The cholinergic and histaminergic systems regulate the level of awareness. The adrenergic system enables the organism to rapidly increase its activity level depending upon the necessities of actual circumstances. The dopaminergic system stimulates the organism to maintain a relatively high activity level on a substantial longer term. The serotonergic system has opposite effects. It mediates relaxation and recuperation.

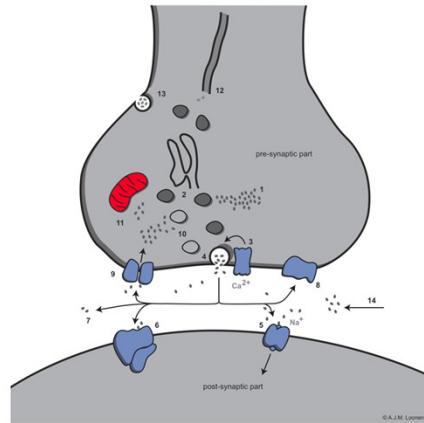
In simple words:

Norepinephrine: rapid acceleration from 0 to 100 km/hr

Dopamine: finishing the marathon well in time

Serotonine: taking some rest while dozing

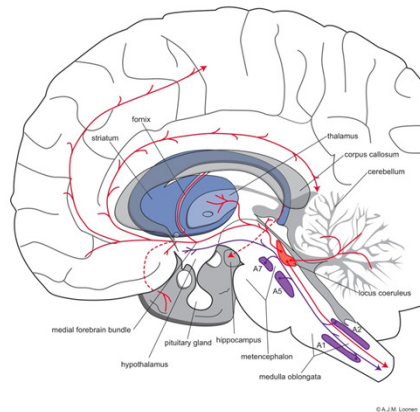
## Antidepressant drugs



- > Reuptake inhibitors
  - Norepinephrine
  - Serotonin
  - Dopamine (minor)
- > Release promoters
  - Norepinephrine
  - Serotonin
  - Dopamine (sometimes)
- > MAO Inhibitors
  - Norepinephrine
  - Serotonin
  - Dopamine (classical MAOI)

Antidepressant drugs interfere with the process of neurotransmission within the synapse. Most antidepressants increase the concentration of neurotransmitter in the synaptic cleft by inhibiting its reuptake; tricyclic and a few dual action antidepressants of norepinephrine and 5-HT, and selective serotonin reuptake inhibitors of only the latter neurotransmitter. Bupropion is an example of an antidepressant also inhibiting dopamine reuptake. Psychostimulants are release promoters, but these drugs are not really suitable to treat depression. An example of an antidepressant which stimulates the release of norepinephrine and serotonin is mirtazapine. MAO inhibitors diminish the oxidative deamination of neurotransmitters after their reuptake from the synaptic cleft. More neurotransmitter will be stored within presynaptic grana, which means that more substance is released during the next depolarization of the terminal. Classical MAO inhibitors like tranylcypromine inhibit the catabolism of both norepinephrine, serotonin, and dopamine. The selective MAO-A inhibitor moclobemide only inhibits the decomposition of the first two neurotransmitters.

## Adrenergic system (norepinephrine)

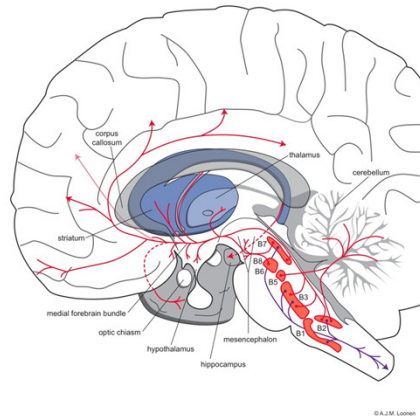


- > Brainstem nuclei
  - Locus ceruleus complex
  - Other (autonomic system)
- > Diencephalic projections
  - $\alpha$ -adrenoceptors
  - emotional response
- > Cortical projections
  - $\beta$ -adrenoceptors
  - cognitive response

Norepinephrine was the first neurotransmitter which was thought to be involved in the mechanism of action of antidepressants. All cell bodies of this small neurotransmitter system are localized within the brain stem. About half of them in the locus coeruleus and the rest of them in a set of nuclei that regulate the activity of part of the autonomic nervous system. Fibres of the adrenergic neurons run to the diencephalon. These fibres are believed to be involved in regulating the emotional and neuro-endocrine responses, Another set of fibres run from the brain stem to the cerebral cortex through the medial forebrain bundle. According to this heavily simplified model, the fibres running to the hypothalamus activate  $\alpha$ -adrenoceptors and fibres running to the cerebral cortex  $\beta$  receptors. These last projections regulate for example the cognitive response.



## Serotonergic system (5-HT)

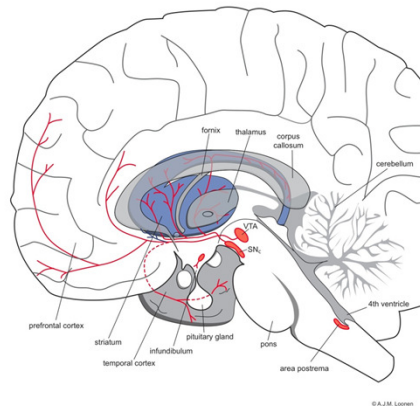


- › Brainstem nuclei
  - Midline (raphes)
- › Brainstem projections
- › Diencephalic projections
- › Forebrain projections
  - Basal ganglia
  - Hippocampus
  - Cerebral cortex

The cell bodies of the serotonergic neurons are also located in the brain stem and as they are found in the neighbourhood of the midline (the raphes) these nuclei are termed the raphe nuclei. Serotonergic fibres are distributed somewhat more widely than their adrenergic equivalents. They run to the spinal cord, several brain stem nuclei, the cerebellum, and the diencephalon (hypothalamus). Forebrain structures that are innervated by these structures are the basal ganglia, the hippocampus and the cerebral cortex.



## Dopaminergic system

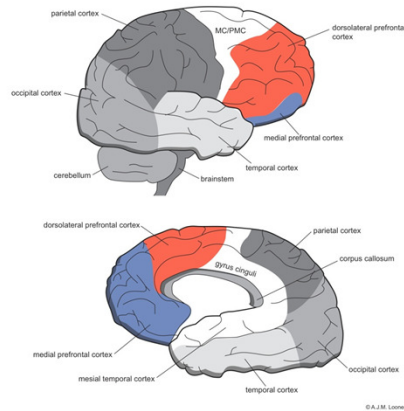


- › Midbrain nuclei
  - Substantia nigra
  - Ventral Tegmental Area
- › Forebrain projections
  - Basal ganglia
  - Mesial temporal cortex
  - Frontal cortex

In the central nervous system three groups of nuclei can be recognized which contain the cell bodies of dopaminergic neurons. Within the caudal part of the medulla oblongata the area postrema is situated. Within the most ventral part of the hypothalamus a group of cell bodies near the eminentia mediana is found. The most important group of cell bodies within the context of this presentation is located in the midbrain. This latter structure contains three areas numbered A8, A9 and A10. The latter two correspond to the substantia nigra pars compacta (indicated by SNc) and the Ventral Tegmental Area (indicated by VTA). From here fibers run to the dorsal and ventral striatum, to the prefrontal cortex and to the mesial part of the temporal lobe. Previously, nigrostriatal (dorsal striatum), mesolimbic (ventral striatum) and mesocortical (cerebral cortex) projections were distinguished, but nowadays these divisions are no longer applied.



## Mechanics of the Mind



### > Cerebral cortex

- Frontal (50%)
- Parietal
- Occipital
- Temporal
- Insular (4%)

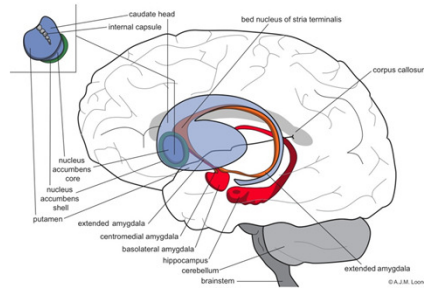
### > Sub-cortex

- Basal ganglia
- Amygdala
- Hippocampus

The central nervous system consists of a spinal cord, brain stem, cerebellum and forebrain. This last structure is called cerebrum in Latin and regulates cognitions and emotions. It consists of two hemispheres connected with each other and the extensive thalamus. The thalamus is a nuclear complex located in the diencephalon and comprising of four parts (the hypothalamus, the epithalamus, the ventral or peri-thalamus, and the dorsal or proper thalamus).

Each hemisphere consists of an outer layer of cerebral cortex with a thickness of about 4 mm and an inner part called the sub-cortex. The cerebral cortex is divided into four parts which are named after the skull-bones they adjoin and a fifth lobe; an insula that is on the outside covered by the temporal lobe. In humans, about 50 per cent of the cerebral cortex is formed by the frontal cortex that in turn consists of three divisions: the motor cortex, the dorsolateral prefrontal cortex (in red) and the medial prefrontal cortex (in blue). The insula is the smallest part; it covers only about 4 per cent of the cerebral cortex.

## Mechanics of the mind



### > Cerebral cortex

- Frontal (50%)
- Parietal
- Occipital
- Temporal
- Insular

### > Sub-cortex

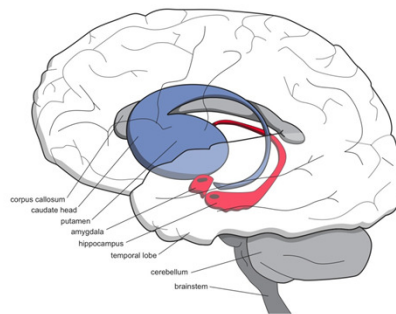
- Basal ganglia
- Amygdala
- Hippocampus

This slide shows you the sub-cortex. The sub-cortex is continuous with the midline structures and in that manner connected to the brainstem. It consists of the archicortex (paleocortex) and the basal ganglia. The basolateral part of amygdala and the hippocampus can be considered to be primitive cerebral cortical tissue. The centromedial part of the amygdala, the extended amygdala, the striatum and the pallidum (not shown) are the main basal ganglia.

In blue, on this slide, is the striatum which consists of the caudate nucleus, the putamen and more ventro-medially of this dorsal striatum; the ventral striatum or Nucleus accumbens. This Nucleus accumbens is macroscopically distinguishable in rodents but diffusely present in the forebrain of humans. It plays an important role in the regulation of motivation and experiencing reward.



## Mechanics of the mind

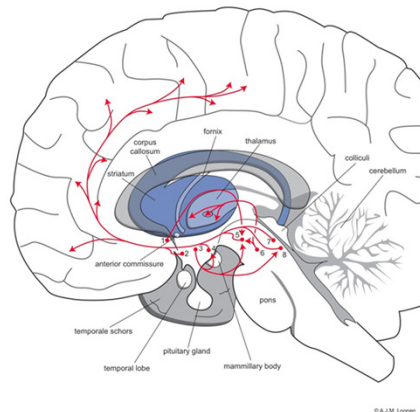


- › **Posterior cerebral cortex (dorsal)**
  - Analysis of input
  - Hippocampus/amygdala
- › **Anterior cerebral cortex (ventral)**
  - Generation of output
  - Hippocampus/amygdala

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Also important within the context of this lecture is to remark that the cerebrum can be divided functionally into a posterior and anterior half. The input to the brain is received and dealt with by the posterior half and the output is generated and released from the anterior half. The entire frontal part of the cerebral cortex belongs to the output generating cortex, apart from the most posterior part of the orbitofrontal cortex and its boundaries with the insula. The hippocampus and the basolateral amygdala can be considered to belong to both input and output cortices.

## Mechanics of the mind



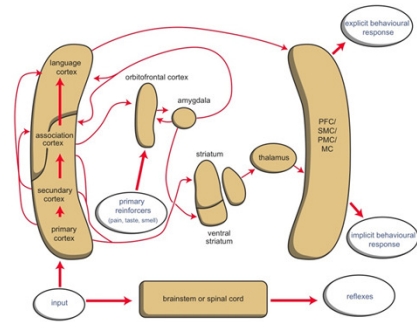
### › Activating systems

- Norepinephrine
  - Rapid increase of activity
- Serotonin
  - Relaxation and recovery
- Dopamine
  - Motivation and initiative
- Histamine
  - Increase of efficiency

On this slide the ascending activating systems are shown. Two of those systems are distinguished: in the upper brain stem the ascending reticular activating system (ARAS) and within the basal forebrain the ascending basal telencephalic system (BTAS). In addition to acetylcholine, GABA and hypocretin/orexin, which will not be discussed here, both norepinephrine, serotonin, dopamine as well as histamine play an important role in these systems. Norepinephrine, dopamine and histamine increase activity, but serotonin has generally speaking an inhibitory influence. The two activating systems are interconnected and influenced by the monoamines involved. The ARAS inter alia stimulates the thalamus, a structure that can be considered to be the gate to the cerebral cortex. The BTAS stimulates the cerebral cortex itself.

## Mechanics of the mind

### › Output of the brain



- Reflexes
- Implicit response
  - Involuntary
  - Unplanned
  - Emotional
- Explicit response
  - Voluntary
  - Planned
  - Cognitive

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In its most essential form behavior can be considered to be an adaptive reaction of the organism to important stimuli from the environment. Within the brain, input from the senses (in man also cognitions) is transformed into a specific, partly behavioral, output as a reaction to the conditions within the individual's biosphere.

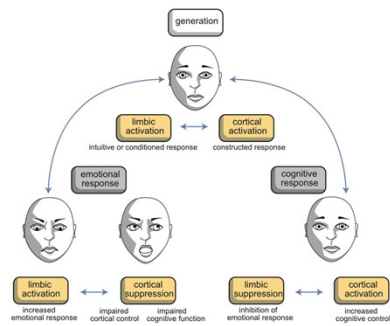
This process is shown on this slide. Input to the spinal cord and brain stem can result in simple reflexes. However, processing the same and other input within the forebrain results in far more complex output. Partly this response is involuntary and automatic, partly this response is voluntary and carefully planned, and mostly it is a combination of these two. In this lecture we call the implicit behavioral response 'emotional' and the explicit response 'cognitive.' This is only to give these processes clearly different names.

We apply these two theoretical response types to a simplified situation which could have been existing in a very ancient world: a primitive man reacting to a novelty in his biosphere.

## Mechanics of the brain

### › Output of the brain

- Reflexes
- Implicit response
  - Involuntary
  - Unplanned
  - Emotional
- Explicit response
  - Voluntary
  - Planned
  - Cognitive



In order to explain the genesis of depression, we want to postulate a model in which man has two possibilities to respond to a novel and potentially threatening, or anadvantageous, situation: to the right a cognitive and to the left an emotional one. Both result in a suitable motor response. When the situation is unclear, and there is no time to analyze all the pros and cons of a carefully planned response, an intuitive response is initiated: like 'duck' or 'run for your life'. In this case, a possible cognitive response is inhibited and priority is given to a pre-programmed emotional response. This corresponds to the inhibition of the dorsolateral prefrontal cortex and to facilitation of the limbic cortex.

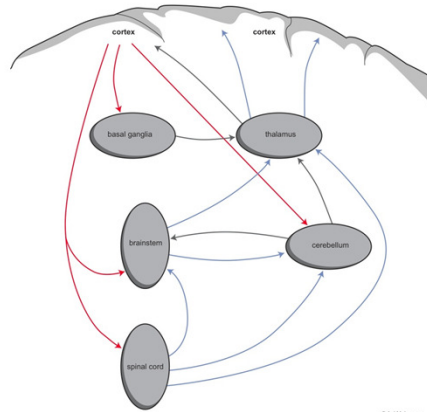
However, when the situation is clear, e.g. when a predator is watching its game, the emotional response is inhibited and all priority is given to the cognitive response. In this case, the functioning of the dorsolateral prefrontal cortex is facilitated.

We hypothesize that the controller of this process of response selection is localized in the medial prefrontal cortex. This structure inhibits the amygdala and therewith decreases the emotional response.





## Mechanics of the mind



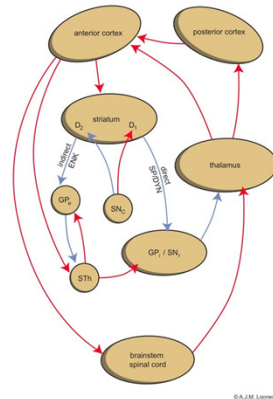
### › Generation of output

- **Direct control**
  - Pyramidal system
- **Gross correction**
  - Cerebro-cerebellum
  - Spino-cerebellum
  - Vestibulo-cerebellum
- **Fine tuning**
  - Basal ganglia
  - Extrapyrmidal circuit

Let us first consider the cognitive response type. For the sake of simplicity, we will only consider motor output as an example. The desire or urge to generate motor behavior, and the plan to realize it, is a function of the prefrontal cortex. The development of a motor program and the commanding of the motor pattern generator (MPG) in the brainstem or spinal cord is a function of the supplementary motor (SMA), premotor (PMA) and motor (MA) cortices. However, this output should also be feedback regulated, dependent upon the input from the outer world and the situation within the individual's body. The gross correction of the motor output is taken care of by the cerebellum and the fine tuning is a function of a system that we used to call the extrapyramidal system. Actually, a more proper name would be the cortico-striato-thalamo-cortical circuit, as we will see subsequently.



## Mechanics of the mind



### › Fine-tuning of output

- **Extrapyramidal circuit**

- Cerebral cortex
- Striatum
- Pallidum
- Thalamus
- Cerebral cortex

- **Major parallel circuits**

- Cognitive (caudate)
- Motor (putamen)
- Motivational (accumbens)

This cortico-striato-thalamo-cortical or CSTC circuit's primary function is to realize that the cortices' output becomes its own input. Depending upon the activity within this circuit, the output of the cortex can be increased or decreased. We will see later on that the activity within the circuit is regulated by dopaminergic fibers originating from midbrain nuclei (SNc, VTA).

## Mechanics of the mind

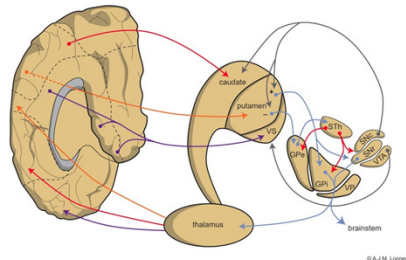
### › Fine-tuning of output

#### • Extrapyramidal circuit

- Cerebral cortex
- Striatum
- Pallidum
- Thalamus
- Cerebral cortex

#### • Major parallel circuits

- Cognitive (caudate)
- Motor (putamen)
- Motivational (accumbens)

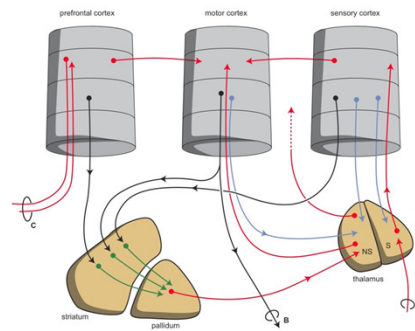


Actually, the CSTC circuit is not only one single loop, but rather a complete set of parallel circuits. These parallel rings can be divided into at least three major sections:

- A cognitive section in red starting in the parieto-occipito-temporal association cortex and running through the caudate nucleus and other basal ganglia to the dorsolateral prefrontal cortex.
- A motor section in orange starting in the somato-sensory parietal cortex and running through the putamen and other basal ganglia to the motor cortex, and
- A motivational section in purple starting in archi- and mesocortical limbic areas and running through the accumbens nucleus and other basal ganglia to the medial prefrontal cortex.

This figure is not entirely correct. The figure is only shows the posterior part of the circuits.

## Mechanics of the mind



### › Fine-tuning of output

- **Extrapyramidal circuit**

- Cerebral cortex
- Striatum
- Pallidum
- Thalamus
- Cerebral cortex

- **Major parallel circuits**

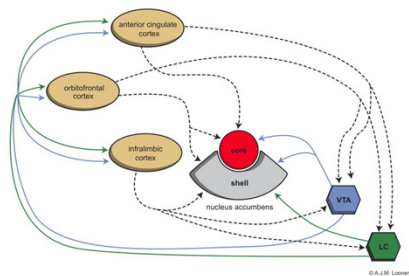
- Cognitive (caudate)
- Motor (putamen)
- Motivational (accumbens)

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Actually, within every circuit information from different anterior and posterior parts of the cerebral cortex converges to a specific point of the frontal cortex. This also results in a few re-entry circuits within the prefrontal cortex, where the respective CSTC circuit both starts and ends. We will come back to this later.



## Mechanics of the mind

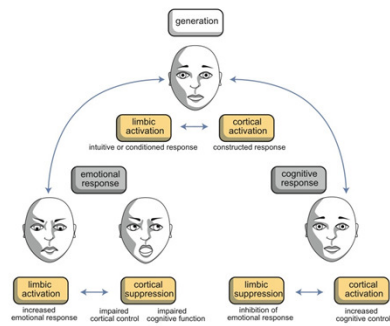


### › Stimulation of response

- Cognitive response
  - NAc<sub>C</sub>
- Emotional response
  - NAc<sub>S</sub>

The most ventral CSTC circuit runs through the Nucleus accumbens. This circuit regulates the intensity of the desire or urge to generate specific motor behavior. The nucleus accumbens has two parts. The core part regulates the motivation to exhibit 'cognitive' type behavior that will finally result in a reward feeling. This core part receives input from the anterior cingulate cortex and the orbitofrontal cortex. The shell part regulates 'emotional' type behavior of which the outcome is uncertain. The shell part receives also input from the orbitofrontal cortex, but additionally from the infralimbic cortex. The infralimbic cortex is situated below the genu part of the Corpus callosum on the mesial side of the prefrontal cortex. It is also called Subgenual Anterior Cingulate Cortex or Brodmann area 25.

## Emotional response $\longleftrightarrow$ Cognitive response



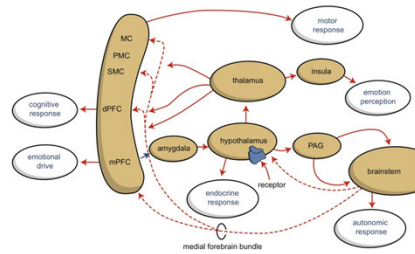
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Now we return to this slide. When man is confronted with novel, uncertain information, which possibly indicates a threat, the shell part of the Nucleus Accumbens stimulates defensive, fight or flight behavior. When man is confronted with novel information, that is probably indicating possible reward, the core part of the Nucleus accumbens stimulates cognitive, catch as you can, behavior.

Let us now consider how the emotional fight or flight response is regulated, because this differs from the regulation of a planned motor response.

## Mechanics of the mind

### > Emotional response



- **Hypothalamus (= controller)**

- Endocrine component
- Autonomic component
- Cortical component

- **Amygdala (= initiator)**

- Posterior cortex
- Hippocampus
- Medial PFC

At this point of our lecture we can introduce the ideas of Terence and Mark Swards (2003) about how the central nervous system regulates certain vital emotions like sexual desire, hunger, thirst, and fear. They describe how the medial and preoptic areas of the hypothalamus play a central role as a controller of these emotional behaviors. Every regulatory scheme consists of three different components.

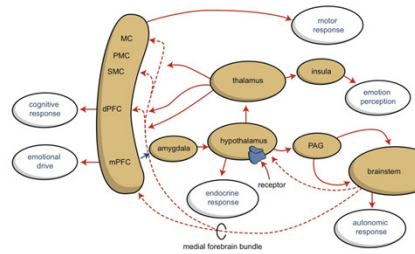
- Firstly, the hypothalamus influences the periaqueductal grey and thereafter other brain stem structures. This activation results in the initiation of the autonomic component of the emotional response. Moreover, the cerebral cortex is influenced by e.g. adrenergic and serotonergic projections from the brainstem.

- Secondly, the medial part of the hypothalamus also influences the lateral endocrine part of this diencephalic structure. This results in the endocrine component of the emotional response.

- The third component is activated by fibers running from the medial hypothalamus to midline and intralaminar nuclei of the thalamus. This results in the motor component of the emotional response (e.g. the startle reaction). Moreover the thalamus influences the dorsolateral prefrontal cortex in order to stop the cognitive plans that were currently in progress. Finally, parts of the mesial prefrontal cortex is activated which results in a drive to respond.

## Mechanics of the mind

### › Emotional response



- **Hypothalamus (= controller)**

- Endocrine component
- Autonomic component
- Cortical component

- **Amygdala (= initiator)**

- Posterior cortex
- Hippocampus
- Medial PFC

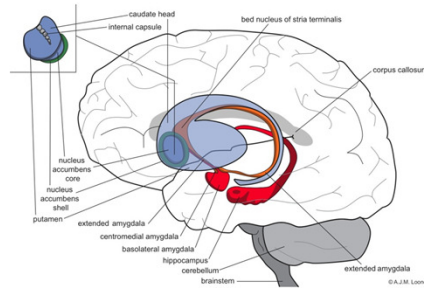
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For some of the emotional response types the amygdala serves as the initiator. This is for example the case in initiating the fear and the anger scheme. The amygdala receives information directly from the posterior cortex, from the hippocampal complex and from the medial prefrontal cortex. This last structure mainly inhibits the amygdala's activity.

The model of Swards and Swards (2003) describes the hypothalamus as a structure that controls the proper execution of the different emotional response types. In this model the hypothalamus contains a set of predefined schedules that only have to be executed when activated upon proper grounds. At least for the flight and fight reactions these proper grounds are determined by the amygdala.



## Mechanics of the mind



### › Limbic cortex

- Infralimbic cortex
- Orbitofrontal cortex
- Basolateral amygdala

### › Limbic sub-cortex

- Centromedial amygdala
- Extended amygdala
- Bed nucleus Stria terminalis
- NAc<sub>bs</sub>

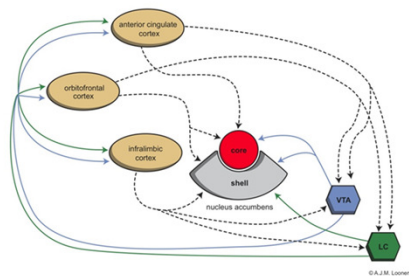
The amygdala may be the most important structure to initiate the considered emotional response types, but does not stand on its own in sustaining these anger/rage or anxiety/fear emotional reaction types.

The amygdala is a complex of nuclei in the pole of temporal lobe that consists of two divisions with a different embryological origin. The basolateral part has a cortical structure and serves as an input channel. This part inter alia receives information from the mesial temporal complex (the hippocampal complex) and from the medial prefrontal cortex. The centromedial part has a basal ganglionic structure and serves as an output channel. This part inter alia gives rise of signals to the hypothalamus.

The basolateral part of the amygdala can be considered to belong to the limbic cortical areas. It plays an important role in deciding which reaction type should be exhibited. The centromedial part of the amygdala can be considered to belong to the limbic basal ganglia (colored orange in this figure), together with the extended amygdala, the bed nucleus of the stria terminalis and the shell part of the Nucleus accumbens. These ganglionic structures play an important role in facilitating these emotional reaction types.



## Mechanics of the mind

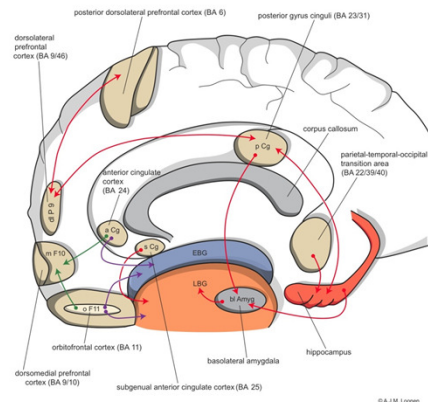


### › Stimulation of response

- Planned response
  - NAc<sub>C</sub>
  - Dopamine
- Emotional response
  - NAc<sub>S</sub>
  - Dopamine/norepinephrine

This brings us back to this figure. The centromedial amygdala belongs to the limbic basal ganglia as is the shell part of the Nucleus accumbens. As was discussed before the nucleus accumbens acts as an interface between the limbic and motor systems and facilitates either the automatic emotional or more the planned motor response. What is also shown in this figure is that both parts of the accumbens receive dopaminergic fibers from the blue VTA, the ventral tegmental area, in the midbrain. It is only the shell part of the Nucleus accumbens which also receives norepinephrine containing fibers coming from the adrenergic locus coeruleus in the hindbrain. So dopamine stimulates both emotional and planned response types and norepinephrine primarily the emotional response.

## Mechanics of the mind



### > Facilitation planned response

- Extrapyramidal CGTC circuit
- Re-entry OFC and ACC
- **Dopamine** stimulates

### > Facilitation unplanned response

- Limbic CGTC circuit
- Re-entry OFC and sCG (BA25)
- **Dopamine** stimulates
- **Norepinephrine** stimulates

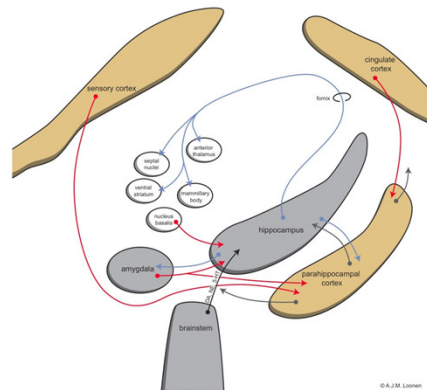
The foregoing explanations are integrated in this figure, which we have already shown at the beginning of this lecture. In this figure we distinguish two cortico-ganglio-thalamo-cortical circuits. In blue the extrapyramidal circuit is shown, regulating the activity of newer parts of the frontal cortex. This circuit facilitates motor behavior that finally leads to improvement of the individual's situation and what is related to reward feelings. Within this circuit two re-entry rings can be distinguished starting and ending within the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC).

In orange the limbic circuit is shown. This circuit regulates the activity of phylo-genetically older parts of the frontal cortex. This loop facilitates behavior which finally results in the escape from threats to the individual's wellbeing. The two re-entry rings which belong to this limbic circuit start and end in the orbitofrontal cortex (OFC) and the subgenual anterior cingulate or infralimbic cortex (sCG).

These two circuits are neither functioning independently from one another nor from the rest of the forebrain. Sensory input to the posterior part of the cerebral cortex is conveyed stepwise to more anterior sites of the cerebral cortex and simultaneously to corresponding parts of the basal ganglia. This results in a well integrated activation pattern of both the frontal cortex and the relevant cortical-subcortical circuits.



## Another role of serotonin



### > Amygdala

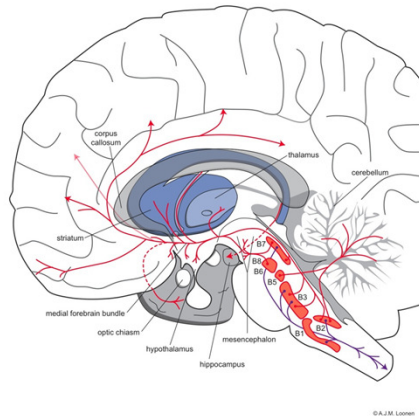
- Basolateral part
- Sensory information
- Mesial temporal complex
  - Hippocampus

### > Hippocampus

- Sensory information
- Recognition
- Output to amygdala
- Output to cortex

However, serotonin has also another influence; it affects the functioning of the hippocampus and amygdala. The amygdala receives input from different parts of the cerebral cortex, including the sensory association cortex and the parahippocampal region. The hippocampal complex plays an important role as a controller of declarative memory formation. Within the hippocampal region sensory information is identified as either having occurred before or as being new and unexpected. Therefore, the hippocampus is considered to be the controller of the memorization process. Moreover, the hippocampal complex has an important influence on the amygdala. The initiation of an emotional response is either facilitated (warning: unidentified, potential harmful situation) or inhibited (relieve: innocent object, no thread). When a potential harmful object is identified, also inhibition of the emotional response can occur and facilitation of a cognitive defense reaction may follow, the hippocampal complex gives output to different parts of the (pre)frontal cortex. a chronic dysfunction of the hippocampus may result in a chronic state of hyperarousal and fear. Serotonin has complex effects on the functioning of the hippocampus.

## Influence of serotonin on hippocampus



- › Direct influence
  - 5-HT<sub>1A</sub> receptors
- › Inhibition of corticoid
  - neuroplasticity

Serotonin has complex effects on the functioning of the hippocampus: it prevents dysfunctioning of the hippocampus by directly stimulating serotonin type 1A receptors and it inhibits the effects of glucocorticoid receptors. These glucocorticoid receptors induce hypoplasia of the hippocampus and SSRIs are known to protect the hippocampal neurons against this influence. It is possible that these two effects are strongly interrelated. However, also other biological responses may also result from the stimulation of serotonin type 1A receptors.

As a consequence, according to this model, serotonin promotes adequate functioning, or it relieves inadequate functioning, of the hippocampal complex. Such an effect would result in an inhibition of the amygdala to induce an inadequate emotional response. As a result of such an action, the cognitive response gets a proper chance to take over. This would result in a relief of the emotional disorder, whether it is a mood disorder or an anxiety disorder. Such a mechanism would correlate with the high efficacy of SSRIs in combination with cognitive behavioral therapy (CBT). SSRIs facilitate the possibility of the prefrontal cortex to adopt cognitive schemes that limit the stressful depressive response.



## Perception of emotions

### › Pleasure

- Decrease of motivation of rewarding behaviour
- Sudden relieve of craving for reward
- Sudden decrease activity OFC and anterior insula

### › Happiness

- Decrease of motivation of stress relieving behaviour
- Sudden relieve of dysphoria
- Sudden decrease activity of sCg and anterior insula

The two described circuits also correspond to two different feelings: pleasure and happiness.

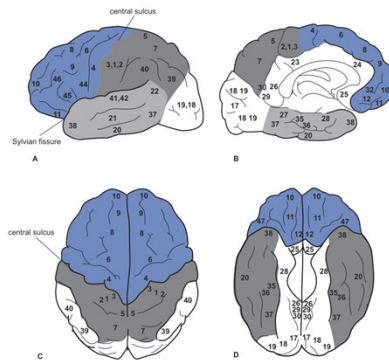
High activity of the motivational ventral striatal circuit results in a strong urge to exhibit reward seeking behavior. This urge corresponds to a feeling of craving for obtaining the effects of illicit drugs. The sudden relief from this urge results in experiencing pleasure.

High activity of the emotional ventral striatal circuit results in a strong urge to escape from this threat to the individual's well being. This urge corresponds to a feeling of dysphoria.

The sudden relief from this urge results in a feeling of happiness.



## The prefrontal cortex in depression



### > Hypoactivity

- Dorsolateral PFC (area 9, 10, 46)
- Ventral/orbitofrontal PFC (area 10, 11, 47)

### > 'Hyperactivity'

- Subgenual cingulate (area 25)

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Although the exact mechanism has not been elucidated, it is clear that depression is accompanied by a dysfunction of the prefrontal cortex.

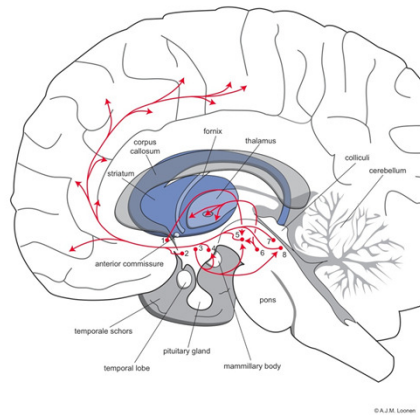
Resting-state PET and SPECT studies in patients with primary depression consistently show a decreased frontal lobe function. The anatomical localization involves both the dorsolateral prefrontal cortex (Brodmann's areas 9, 10 and 46) and the ventral prefrontal and orbitofrontal cortices (Brodmann's areas 10, 11, and 47). Hypoactivity in the dorsolateral areas may correspond to apathy and cognitive dysfunctioning.

A third prefrontal structure that has been implicated in negative mood states is the subgenual part of the anterior cingulate cortex (Brodmann's areas 25 and the caudal portions of Brodmann's areas 32 and 24). Anatomical studies have shown that the volume of the sCg is reduced in certain depressed groups. Moreover, the activity of the sCg is affected following successful treatment with SSRIs, electroconvulsive therapy, transcranial magnetic stimulation (rTMS), ablative surgery and deep brain stimulation. However, this sCg has been found to be metabolically overactive in depressed states and reacts to treatment with a decrease of its activity.

These findings indicate, that in depression two processes contribute to pathophysiology. Firstly, the previously described hypofrontality corresponds to lack of motivation to exhibit rewarding behavior. This is accompanied by the inability to experience pleasure. Secondly, the hyperfunction of the subgenual anterior cingulate corresponds to an increased motivation to escape from threats to well being. This is accompanied by feelings of dysphoria, which is the opposite of happiness.



## Model for depression



- › Norepinephrine
  - Hypothalamus ( $\alpha$ )
  - Frontal cortex ( $\beta$ )
- › Serotonin (5-HT<sub>2</sub>)
  - Inhibits norepinephrine
  - Inhibits dopamine
- › Serotonin (5-HT<sub>1a</sub>)
  - Stimulates hippocampus
- › Dopamine (D<sub>1</sub>)
  - Medial PFC
  - Dorsolateral PFC

This slide summarizes how the adrenergic, serotonergic, and dopaminergic systems affect the functioning of the forebrain. As shown, serotonin inhibits the adrenergic and dopaminergic systems and in addition stimulates the functioning of the hippocampus. This brings us to the essentials of the amine hypothesis of depression.





## Conclusion amine hypothesis

- › Norepinephrine acts on hypothalamus
- › Serotonin acts on hippocampus
- › Dopamine acts on prefrontal cortex
  
- › Lag time due to gradual effects
  
- › All systems are interconnected !

Antidepressant drugs can influence depressive disorder because they stimulate adrenergic neurotransmission within the hypothalamus and/or serotonergic neurotransmission within the hippocampus. Some of them also influence dopaminergic transmission which results in stimulation of certain parts of the prefrontal cortex. The lag time between the pharmacological and clinical effects is caused by the time it takes for the changes in functioning become effective. It should be considered that the adrenergic, serotonergic and dopaminergic systems are heavily interconnected. It is not possible to influence one system without affecting the other.



## Pathophysiology of depression

- › Amine hypothesis
- › **Biorhythm hypothesis**

Mood disorders can also be considered as biorhythm disorders. This brings us to the second theory of the genesis of mood disorders.



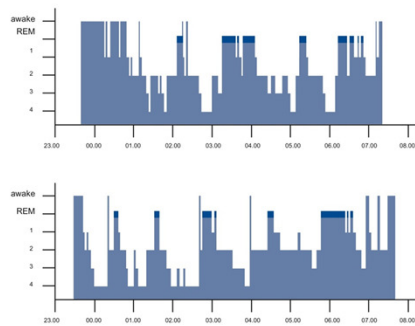
## Biorhythm dysregulation

- › Sleep disturbances in depression
  - REM sleep latency
  - Sleep architecture
  - Late night insomnia
- › Day time fluctuations
- › Disturbed biological rhythms

Several aspects of the symptomatology of depression indicate that something is wrong with the biological clock. Depressive disorders are well known to be accompanied by sleep disturbances. In patients with a depressive disorder the time period between the moment they fall asleep and the moment that the first REM sleep occurs, is remarkably shorter than in non-depressed humans. In some individuals REM sleep even occurs instantaneously. This is reflected by an astonishing distortion of the sleep architecture, i.e. the sequence of sleep stages during the night. Moreover, depressed patients suffer from an interrupted sleep and late night insomnia. Apart from these sleep disturbances other biorhythm disorders are evident. In depressed patients mood and other symptoms show a typical fluctuation of severity during the day. In the morning they feel worse and during the course of the day things go slightly better. Also other biorhythms, such as body temperature and the cortisol rhythm, become irregular.



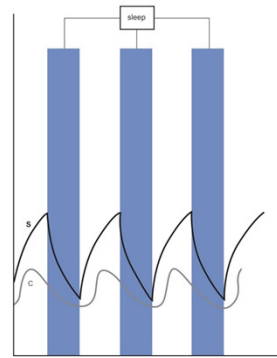
## Hypnogram



- › Depressed patient
  - Before treatment
- › The same patient
  - After recovery

The sleep disorders can be illustrated by comparing a hypnogram of a depressed patient before and after treatment with ECT. A hypnogram is a graphic representation of the sleep stages that occur during sleep. It is based upon the EEG activity that is exhibited by the sleeping brain. After falling asleep a person's sleep initially becomes deeper and deeper. After having spent a period in sleep phase IV (deep sleep or slow wave sleep), sleep becomes lighter again and a period of paradoxal sleep or REM sleep follows. In normal adults, it takes about 1.5 hours to pass through such a sleep cycle. During the night several sleep cycles are passed through. The hypnogram of a depressed patient is entirely different. The sleep phases are irregularly distributed. In this patient, the first REM sleep phase occurs rather late, but that is not typical. What is evident is that the sequence of sleep phases is abnormal. After recovery, a normal hypnogram is observed.

## Circadian rhythm



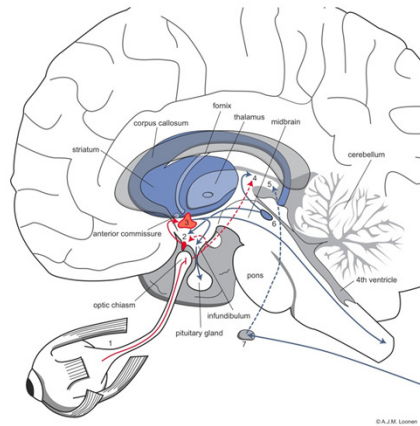
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### > Circadian rhythm

- Body temperature
- ACTH secretion
- Renin secretion

This figure shows the relevant biorhythms during night (in blue) and day (in white). Two rhythms determine the alternating sequence of wakefulness and sleep: i.e. the circadian biorhythm and the somnostatic rhythm. The fluctuations in body temperature and that in ACTH and renin secretion are intricately connected to the circadian biorhythm. Other fluctuations are less clearly linked to the circadian bio-clock. It is hypothesized that a theoretical sleep factor  $S$  is built up, when a person is awake. When a person is active during the day the need to fall asleep is steadily increases. During the night when a person is sleeping the amount of this theoretical sleep factor  $S$  decreases. The person will wake up when sleep factor  $S$  has disappeared to a large extent and simultaneously the circadian rhythm is in a correct phase.

## Circadian rhythm



### › Characteristic of SCN

- Fluctuating rest potential
- Vasopressin (ADH) →  
Nc Paraventricularis (PVN)
  - CRH
  - ADH

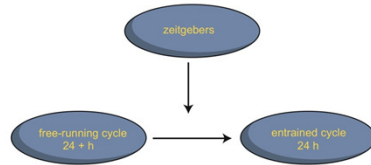
The circadian rhythm is caused by a rhythmic fluctuation of the membrane potential of neurons in the suprachiasmatic nucleus in the hypothalamus. These neurons secrete vasopressin (ADH) from fibres which run to the paraventricular nucleus. This secretion also shows rhythmic fluctuations. Fibers from the paraventricular nucleus release CRH into the primary portal circulation of the pituitary gland. This explains the rhythmic fluctuation of ACTH secretion.



## Circadian rhythm

### › Entraining

- 'Zeitgebers'
  - Morning light
  - Melatonin

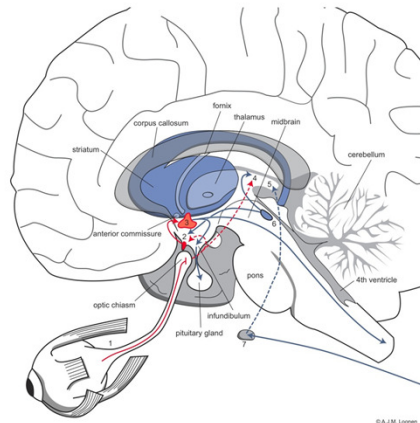


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The genuine circadian biorhythm is established somewhat beyond 24 hours. Therefore, the awakening can become an important 'Zeitgeber' that will reset the circadian rhythm. This daily occurring process is termed 'entraining.' Several other Zeitgebers are active apart from this awakening stimulus, though far less important than awakening. One of them is the hourly pulses with which corticosteroids are secreted from the adrenal glands.



## Suprachiasmatic nucleus



### › Light

- Direct influence
- Melatonin secretion

### › Melatonin

- Mel<sub>1a</sub> receptors in SCN
- Mel<sub>1b</sub> receptors in Retina

Daylight plays the most important role in the entraining process. Although highly simplified and not entirely correct, this can be explained by the following model. Awakening is thought to reset the biological clock of the nucleus suprachiasmaticus (SCN) by full exposure to daylight when the eyes are opened and daytime activity starts. The SCN is directly connected to the retina by fibers that deviate from the optic tract before reaching the thalamus and the cerebral cortex. Therefore, this mechanism is also functioning in cortical blindness, but not in retinal blindness. The sensitivity for the entraining influence of daylight on both the retina and the SCN is enhanced by melatonin. Melatonin is a hormone that is secreted by the pineal gland during sleep provided that this sleep matches with the night phase of the circadian rhythm. The secretion of melatonin is initiated by fibers of a branch of the sympathetic nervous system running from the superior cervical ganglion to the pineal gland. Melatonin binds to specific receptors in the SCN (Mel-1a) and retina (Mel-1b). This explains why treatment with an evening dose of melatonin has therapeutic effects on the biorhythm in patients with a dysfunctioning retina (e.g. retinal blind people). Melatonin increases the entraining influence on the SCN of the first stimulation by daylight at awakening.



## Biorhythm hypothesis

- › Mismatch between biological and natural circadian rhythm
- › ‘Entraining’ disorder
  - Insufficient influence of daylight as ‘Zeitgeber’
  - Insufficient influence of melatonin
- › Depression as hibernation state
- › Biorhythm hypothesis is linked to ...

The biorhythm hypothesis of depression postulates that the depressive symptoms are caused by a dysfunction of the SNC as the generator of a correct circadian rhythm. One hypothesis says that in depression there is a mismatch between the biological rhythm and the true natural rhythm. When the biological rhythm is shorter than 24 hours this mismatch would cause a false start. It is possible that this would cause serious trouble. However, experiments have given contradictory results. Another hypothesis says that in at least some depressed patients an entraining disorder is causing the problems. This may be due to insufficient influence of day light as a ‘Zeitgeber’. In turn this may be related to insufficient stimulation of the retina by daylight or to insufficient sensitivity of the SNC or both. In a subpopulation of depressed patients exposure to bright light has therapeutic effects as well as treatment with an evening dose of melatonin. However, in many depressed patients this is not the case. Therefore, it is not very likely that this mechanism is the primary defect and that depression is comparable with a sort of exaggerated hibernation state in humans. However, it can be suggested that in a subpopulation of patients this mechanism may play a role by inducing neuro-endocrine disturbances that are related to the pathogenesis of depression. This links the biorhythm hypothesis to the ...



## Pathophysiology of depression

- › Amine hypothesis
- › Biorhythm hypothesis
- › **Neuro-endocrine hypothesis**

... neuro-endocrine hypothesis of the depressive disorder.

The neuro-endocrine hypothesis of depressive disorder says that the mood disorder results from a dysregulation of the endocrine system.



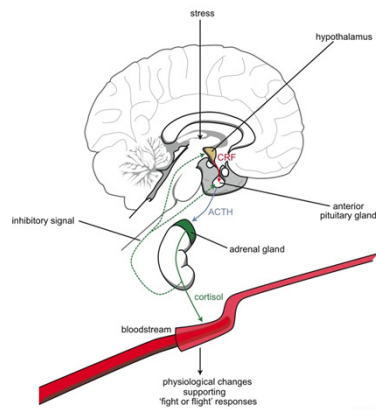
## Neuro-endocrine hypothesis

- › Hypoactivity of the HPT axis
- › Irregular activity of the HPG axis
- › Hyperactivity of the HPA axis
  - Flattened response to CRH
  - Increased cortisol levels
  - Changed circadian rhythm
  - Decreased negative feedback
  - Cell hyperplasia in Nc Paraventricularis
    - CRH, ADH and OXY producing cells
    - CRH/ADH producing cells

At least three endocrine sub systems have been postulated to be candidates for playing an important role in the pathogenesis of depressive disorders. Improper functioning of the thyroid gland and of the endocrine gonads is well known to accompany a variety of mood disturbances. Although this is certainly relevant, it will not be discussed here in further detail.

In this lecture we will concentrate on the HPA axis. Several HPA abnormalities are observed in mood disorders, although they are not always consistently found and seem to be variable in different subgroups of depressed patients. Increased plasma levels of corticosteroids are observed in a large proportion of these patients. In addition, several depressed patients do not respond with the same increase of cortisol levels after the administration of the Corticotrophin Releasing Hormone (CRH). The circadian cortisol rhythm is lost and an exogenous corticosteroid dexamethason is not as active in inhibiting cortisol secretion as in non-depressed persons. These findings indicate that HPA axis is hyperactive and less sensitive to feedback inhibition in patients with a major depression. These changes are nowadays believed to be orchestrated by CRH. It has been demonstrated that the abnormality is already present at the level of the hypothalamus. A hyperplasia is observed in the hypothalamus of paraventricular cells that secrete CRH into the primary portal circulation of the pituitary gland. In reaction, this gland produces more ACTH which stimulates the adrenal glands.

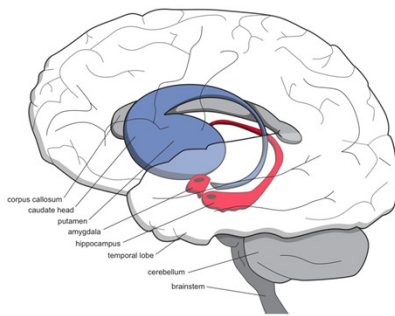
## HPA axis in depression



- > Anatomy of HPA axis
  - PVN produces CRH
  - Pituitary gland produces ACTH
  - Adrenal gland produces cortisol
- > High cortisol level
  - Optimisation of response
    - Increased emotional response
    - Decreased cognitive response
  - Protection against damage
- > Low cortisol level
  - Recovery and repair
  - Response readiness

This sequence is shown in the current slide; hypothalamic paraventricular cells produce CRH which stimulates the pituitary gland to produce ACTH. This hormone stimulates the cortex of the suprarenal glands to secrete cortisol into the general circulation. Cortisol inhibits the hypothalamus and the pituitary gland to secrete CRH and respectively ACTH and therefore gives feedback inhibition. This last process appears to be disrupted in depression.

## Cortisol receptors within the brain

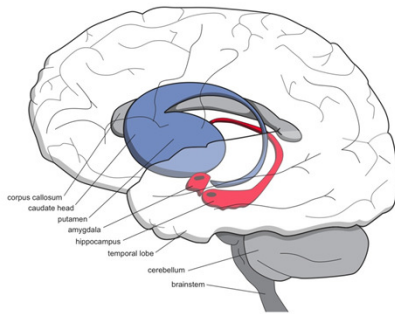


- › Nuclear mineralocorticoid (MR)
  - High affinity receptors
  - Bound at low levels
  - Tonic inhibition & stabilization
  - Pro-active control
- › Membrane MR
  - Low affinity receptors
  - Bound at high levels
  - Rapid response
  - Enhance excitability
- › Nuclear glucocorticoid (GR)
  - Low affinity receptors
  - Bound at high levels
  - Ending stress response
  - Re-active control

Cortisol is secreted from the adrenal glands in hourly pulses, with the largest pulse amplitude at the start of the circadian activity period. Cortisol can penetrate into the brain and has multiple effects depending on its levels. This is due to the presence of two types of cortisol receptors, called mineralocorticoid receptors (MR) and glucocorticoid receptors (GR). These names are not entirely correct because the mineralocorticoid aldosterone poorly penetrates into the brain and therefore does not bind to these MR receptors itself; both receptor types are cortisol (a glucocorticoid) receptors. MR as well as GR receptors are ligand-driven transcription factors functioning in genomic control, acting within the cell nucleus. They are therefore called nuclear receptors. However, within the brain, membrane associated mineralocorticoid receptors are also found. Cortisol has low affinity to these membrane bound mineralocorticoid receptors, so these are only activated by the high levels of cortisol occurring during a stress reaction.

As can be seen on this slide the different cortisol receptors have different functions. Nuclear mineralocorticoid receptors induce tonic inhibition and stabilization of cerebral neurons, while membrane bound mineralocorticoid receptors increase excitability. Nuclear glucocorticoid receptors have the important function of facilitating the return to a normal situation once a stress response has taken place.

## Effects of cortisol within the hippocampus



- › Low levels of cortisol
  - Bound to high affinity nuclear MR
  - Tonic inhibition & stabilization
  - Pro-active control of stress response
- › High levels of cortisol
  - Bound to low affinity membrane MR
  - Rapid response
  - Enhance excitability
  - Immediate facilitation of stress response
- › High levels of cortisol
  - Bound to low affinity nuclear GR
  - Ending stress response
  - Re-active control

The described effects (also) take place in the hippocampus. At low concentrations cortisol stimulates mineralocorticoid receptors which are situated within the cell nucleus. By stimulating these mineralocorticoid receptors cortisol induces recovery and repair and it prepares the hippocampus to give an adequate and rapid response to a stressful situation. At high levels, cortisol is bound to nuclear glucocorticoid receptors. These receptors modify the stress response and thereby optimize this stress reaction. High concentrations of cortisol normalize brain activity some hours after an organism has been exposed to a stressful event and promote consolidation of the event for future use. At the same time high concentrations of cortisol also stimulate low affinity mineralocorticoid receptors which are located in the outer cell membrane. These high levels of cortisol activate the hippocampus to immediately participate in the stress response. In response to this stimulation the hippocampus starts sending signals to other areas including the amygdala and prefrontal cortex. So, high levels of cortisol acutely facilitate the emotional response type and inhibit the cognitive response type. In addition, through stimulation of nuclear glucocorticoid receptors high levels of cortisol simultaneously protect hippocampal cells against possible damage by uncontrolled, heavy activity and limit the stress response on a somewhat longer term.





## Depression, cortisol & hippocampus

- › Effect of depressive disorder (cortisol)
  - Disturbed MR/GR balance
  - Dysfunction of hippocampus
  - Shrinkage of the hippocampus
- › Effect of antidepressant treatment
  - Protection against dysfunction (5-HT<sub>1a</sub>)
  - Protection against hypoplasia (5-HT<sub>1a</sub>)
  - Correction of MR/GR balance

In patients with a depressive disorder a change in the functioning of this mechanism is observed. This has been explained by the Dutch scientist Ron de Kloet by postulating that

- sustained hyperactivity of the HPA-axis on the one hand
- in addition to a MR/GR imbalance which is precipitated by (early) life stress on the other, may generate a phenotype that is vulnerable for depression.

So, the pathological changes in depression are thought to be caused by an imbalance between the functioning of MR and GR receptors in the hippocampus.  
As a consequence of this hypoplasia of the hippocampus occurs, which may reflect a dysfunction of this structure.

As has been said before, the hippocampus is important for the functioning of the declarative memory. When the hippocampus stops identifying objects and events, the emotional response type will dominate the picture. This results in constant activation of the limbic cortico-ganglio-thalamo-cortical circuit in order to escape from this misery.

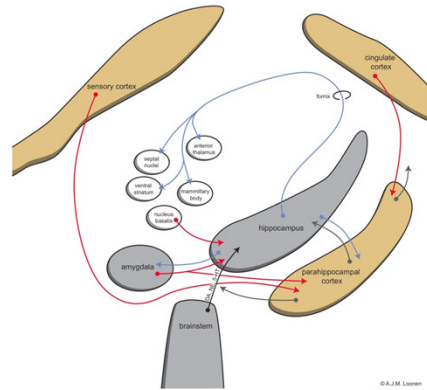


## Depression, cortisol & hippocampus

- › Effect of depressive disorder (cortisol)
  - Disturbed MR/GR balance
  - Dysfunction of hippocampus
  - Shrinkage of the hippocampus
  
- › Effect of antidepressant treatment
  - Protection against dysfunction (5-HT<sub>1a</sub>)
  - Protection against hypoplasia (5-HT<sub>1a</sub>)
  - Correction of MR/GR balance

A few experimental findings indicate that the antidepressive effects of drugs, particularly SSRIs, have something to do with the effects of cortisol on the hippocampus. It has been found that stimulation of 5-HT<sub>1a</sub> receptors protects the hippocampus against cortisol-induced dysfunction as well as cortisol-induced hypoplasia. Through (chronic) stimulation of these 5-HT<sub>1a</sub> receptors, SSRIs seem capable of repairing the MR/GR imbalance. This results in a proper inhibition of the amygdala by sensory information that makes the actual situation harmless and unthreatening and placing the individual at ease again.

## The role of the hippocampus



### › Amygdala

- Basolateral part
- Sensory information
- Mesial temporal complex
  - Hippocampus

### › Hippocampus

- Sensory information
- Recognition
- Output to amygdala
- Output to cortex

This brings us back to this slide, which we have seen before when we were dealing with the role of serotonin. The amygdala gives a signal to the hypothalamus to start or increase an emotional fear/flight or anger/fight reaction on the basis of the input of sensory information to the basolateral part of this complex. This process is facilitated or inhibited by information coming from the hippocampus. The hippocampus is the controller of the identification and memorization process (episodic memory). After identification it gives an inhibitory signal to the amygdala and a stimulatory signal to the prefrontal cortex to plan and execute an adequate cognitively planned response. When the hippocampus dysfunctions due to neuroplastic changes which are induced by cortisol, the amygdala is disinhibited and keeps on activating the emotional reaction type.

### Note:

Apart from this mechanism chronic stress also induces direct neuroplastic changes in the medial prefrontal cortex and in the amygdala. We will return to this phenomenon later.



## Neuro-endocrine hypothesis

- Disturbed MR/GR balance
- Dysfunction of hippocampus
- Inadequate recognition of episodic sensory input
- Inadequate activation of basolateral amygdala
- Inadequate activation of general fear response
- Neuro-endocrine hypothesis is linked to ...

So, when we summarize the neuro-endocrine hypothesis of depression: In depressed patients problems are caused by the existence of a disturbed balance between mineralocorticoid and glucocorticoid receptors which results in a malfunctioning of the hippocampal complex. This leads to inadequacies regarding the recognition of episodic memories. As a consequence the amygdala is too often or too strongly activated to initiate an emotional fear/flight response.

The malfunctioning of the hippocampus is largely based on inadequate neuroplastic effects of cortisol. Cortisol has profound neurotrophic activity and it shares this capacity with the so-called cytokines which are produced by immune-competent cells. In addition, the functioning of the HPA axis and the immune system are intricately interconnected. This brings us to the description of the related ...



## Pathophysiology of depression

- › Amine hypothesis
- › Biorhythm hypothesis
- › Neuro-endocrine hypothesis
- › **Neuro-immune hypothesis**

... neuro-immune hypothesis of depression.

Essential to the neuro-immune hypothesis is the observation that the immune system is intricately connected to the functioning of the central nervous system. This is partly mediated by the interaction between the HPA axis and the immune system, partly by a direct interaction between neurons and immune cells.

This complicated interaction between nerve cells, endocrine cells and immune cells is regulated by chemical substances. We have already dealt with neurotransmitters secreted by neurons and hormones secreted by endocrine cells, but until now did not mention cytokines; the substances which transfer the messages of immune cells. Similar to cortisol many cytokines exert neuroplastic effects, which make them special type neurotrophic factors. Similar to other neurotrophic factors they exert a profound action on the functioning of nerve cells. Neurotrophic factors are known to enhance or limit the sprouting of axons and dendrites and the formation of new branches and projections. Moreover, when one nerve cells makes contact with another neuron, the influence of specific neurotrophic factors modifies the contact spot into a regular synapse and regulates its activity. So, neurotrophic factors change the structure of the central nervous system on a micro scale and cytokines may be an example of substances having this type of effect.



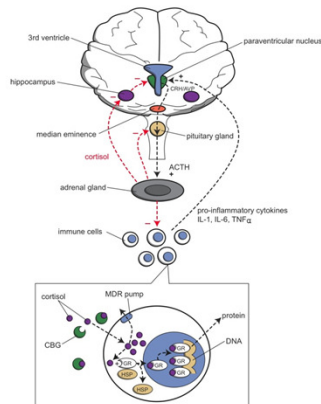
## Neuro-immune hypothesis

- › Increased inflammation in depression
  - Raised pro-inflammatory cytokines
    - IL-1, IL-6, C-reactive protein, TNF- $\alpha$
  - Lowered anti-inflammatory cytokines
    - IL-4, IL-10
  - Imbalance between inflammatory and anti-inflammatory immune cells/system
- › Inhibition of neuronal repair mechanism
- › Increase in endogenous neurotoxins
- › Neurodegenerative changes

So, an important category of neurotrophic alterations is primarily associated with the functioning of the immune system. And in depression the immune system appears not to function properly. This is reflected by the changes in the blood levels of many pro-inflammatory and anti-inflammatory cytokines. Through these changes depression leads to structural changes which can be considered to be neurodegenerative in nature. This is accomplished directly by neuroplastic effects of cytokines, by inducing the synthesis of neurotoxic substances and by affecting the influence of the HPA hormones.

Concerning this influence of the HPA hormones, we should consider that several lines of evidence suggest that cytokines may contribute directly to insufficient glucocorticoid signaling by diminishing glucocorticoid receptor activity. Administration of cytokines in vivo and in vitro has been shown to reduce both glucocorticoid receptor number and function. These findings may provide a plausible scenario in which glucocorticoid insufficiency contributes to unrestrained cytokine release, which in turn further impairs glucocorticoid receptor functioning.

## Interaction HPA axis & Immune system



### > HPA axis

- Cortisol inhibits (feed back inhibition)
- Cytokines increase

### > Immune system

- Cortisol inhibits cytokine production
- Cortisol induces anti-inflammatory factor

As is shown on this slide, the functioning of the HPA axis and the immune system are mutually dependent upon each other. As was explained a few slides back, cortisol inhibits the hypothalamus in producing CRH and the pituitary gland in producing ACTH. On the other hand, cortisol reacts with intracellular receptors in peripheral immune cells. These complexes translocate to the nucleus and inhibit the immune response either by interacting with other transcription factors or by directly binding to DNA to influence gene transcription. The first results in abolishing the production of cytokines and the second in the production of inhibitors that work as an anti-inflammatory factor. So, cortisol inhibits both the HPA axis and the immune response.

On the other hand, certain pro-inflammatory cytokines, such as interleukin (IL)-1, interleukin (IL)-6 and tumor necrosis factor (TNF)- $\alpha$ , are potent stimulators of CRH release and therefore of the HPA axis. These pro-inflammatory cytokines are produced in the periphery by a variety of immune cells, in response to different stimuli including danger signals and stress. The stimulation of the HPA axis which results from this release limits the activation of the immune response when the danger is eliminated. It has been postulated that aberrant activation of CRH pathways by pro-inflammatory cytokines is at the basis of the over activity of the HPA axis in depression. It therefore represents one of the primary mechanisms by which cytokines contribute to the development of HPA hyperactivity in depression.





## Neuro-immune hypothesis

- › Interaction between CNS and immune system
- › Interaction between HPA and immune system
- › Depression is a chronic inflammatory disease
- › Depression leads to neurodegenerative changes
- › Antidepressants induce repair and reconstruction

Now, let us summarize this complex matter. Essential to the neuro-immune hypothesis is the observation that the immune system is intricately connected to the functioning of the central nervous system. In addition, the HPA axis and the immune system mutually influence each other. These interactions, and the aberrant alterations of them that occur in depressed patients, induce a chronic inflammatory condition of the central nervous system in depression. This leads in turn to structural changes that can be considered to be neurodegenerative in nature and can progress into Alzheimer's disease and other dementias. Antidepressant drugs may protect neurons from these changes by promoting repair and the construction or reconstruction of neuronal networks.



## Peripheral and brain cytokines

- › Cytokines penetrate the brain
  - Crossing blood brain barrier
  - Circumventricular organs
  - Transmission by afferent nerves
- › Cytokines are produced in the brain
  - Astrocytes
  - Microglia cells
  - Vascular endothelial cells
  - Fibroblast

Cytokines have important effects in the central nervous system. Peripheral immune activation is transmitted to the brain by several communication pathways that include saturable transporters of cytokines across the blood-brain barrier, humoral transmission via the circumventricular organs, and neural transmission via afferent nerves, for example the vagal nerve, that innervate the site of the body in which the inflammatory response takes place. This ultimately results in the synthesis and release of pro-inflammatory cytokines in the brain by activated astrocytes, microglia cells, vascular endothelial cells, and fibroblasts.

Moreover, during the last three decades it has become evident that the central nervous system also contains its own immune system. This CNS immune system is actively involved in stress reactions. It also has become clear that an important interaction exists between the CNS and peripheral immune systems on the one hand and between both immune systems and other CNS regulatory systems on the other.

Cytokine receptors are present in the brain, but they are activated in most cases not by peripheral cytokines that enter the brain, but by cytokines that are produced locally within the brain in response to peripheral cytokines. These locally produced cytokines act on other glial cells and ultimately on neurons.

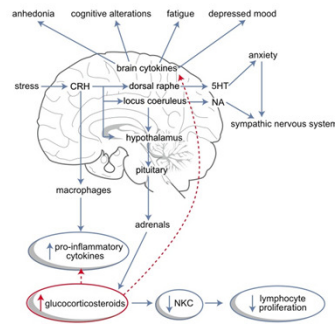


## Interactions mental functions - immune system

- › Mental state alters cytokine production
  - Danger signals and stress (anxiety, depression)
  - HPA axis inhibits inflammatory response
  - Depressive disorder is associated with reduced immune cell activity and increased cytokine production
- › Cytokines give mental symptoms of sickness
  - Apathy and social withdrawal
  - Anhedonia and fatigue
  - Cognitive and mood disturbances

Cytokines form an important link between the immune system and mental functioning. On the one hand, the peripheral cytokine production is influenced by mental processes, either directly (e.g. resulting from an increase of the sympathetic tone) or indirectly through activation of the HPA axis. On the other hand, brain cytokines activate the HPA axis and the neural circuits involved in the regulation of sleep, appetite, metabolism, affect, and cognition. Via their actions in the brain, cytokines are responsible for the occurrence of the non-specific symptoms of sickness, including apathy, social withdrawal, anhedonia, fatigue, and alterations in cognition and mood.

## Interaction Stress & HPA & Immune system



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The complex relationship between stress and cytokines or glucocorticosteroids is summarized in this figure. Stress results in a direct activation of the peripheral immune system on one hand and in a somewhat slower occurring inhibition of the same peripheral immune response by activation of the HPA axis and the sympathetic nervous system on the other hand. Pro-inflammatory cytokines activate the release of brain cytokines, and these activate relevant neuronal circuits but also the HPA axis. Glucocorticoids inhibit the release or function of these pro-inflammatory cytokines and also induce feedback inhibition of the activity of the HPA axis. When this system cooperates correctly the source of stress is dealt with correctly by a self-limiting mechanism.

Depressed patients show elevated levels of corticotropin-releasing hormone. It is a key neuropeptide in the regulation of the response to stress, orchestrating stress-induced activation of the HPA axis (and the release of adrenocorticotrophic hormone and cortisol) and the sympathetic nervous system (and the release of catecholamines). Activation of corticotropin-releasing hormone pathways by pro-inflammatory cytokines represents one of the primary mechanisms by which cytokines may contribute to the development of depression.



## Influence of antidepressant drugs

- › Serotonin acts as a growth factor
- › Serotonin interacts with BDNF
- › Antidepressant drugs increase BDNF
- › Repair and reconstruction of neuronal networks

Serotonin can be considered to offer protection against the damaging influence of the inflammatory process during depression. Serotonin appears to be of huge importance for normal CNS development and function. Serotonin acts as a growth factor during embryogenesis, and serotonin receptor activity forms a crucial part of the cascade of events leading to changes in brain structure. The serotonergic system interacts with brain-derived neurotrophic factor (BDNF). This may explain why antidepressant drugs increase the signaling of BDNF. It has been suggested that the chronic effects of antidepressant drugs are associated with the repair, and possible construction, of neuronal networks. Antidepressants are known to enhance axonal and dendritic sprouting and are believed to stabilize synaptic contacts.



## Neuro-immune hypothesis

- › Influence on neurotransmitters
  - Serotonin
- › Influence on corticosteroids
  - Activity HPA axis
- › Influence on neuroplasticity
  - Cytokines (IL-1, IL-6, TNF)
  - Other neurotrophic factors (BDNF)
- › Influence on excitability
  - Amygdala and hippocampal complex

The neuro-immune hypothesis on the pathogenesis of depression has not yet found its definite form. Several possibilities exist to show how activation of the CNS immune system results in a change of functioning of the central nervous system. We try to explain the genesis of a depressive disorder by concentrating on an inhibition of the functioning of the hippocampus. This may result in an improper stimulation or a disinhibition of the amygdala. Moreover, cytokines have a profound influence on the excitability of neurons. When this phenomenon occurs in the amygdala and is added to an decreased inhibitory input from the hippocampus, a phenomenon termed 'kindling' may occur. This brings us to the last hypothesis for the pathogenesis of the depressive disorder.



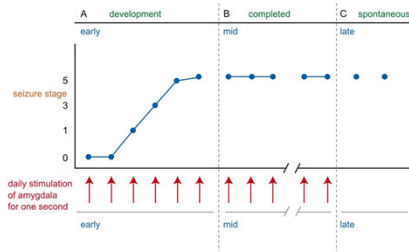
## Pathophysiology of depression

- › Amine hypothesis
- › Biorhythm hypothesis
- › Neuro-endocrine hypothesis
- › Neuro-immune hypothesis
- › **Kindling hypothesis**

The illness progression hypothesis is most often referred to as the 'kindling' hypothesis. This theory says that, analogous to the relationship between kindling and convulsions, some stressors may produce increasing effects over time resulting in a full-blown affective episodes. The more episodes of unipolar or bipolar illness a patient has, the more vulnerable he or she becomes to recurrences and the development of cognitive dysfunction. In the current lecture, we want to take this idea a step beyond this point to a possible explanation for the pathogenesis of depression. But let us first explain the original theory.



## Kindling



### > Development

- Steadily increasing activity
- Behavioural seizures

### > Completed

- Generalized motor seizures

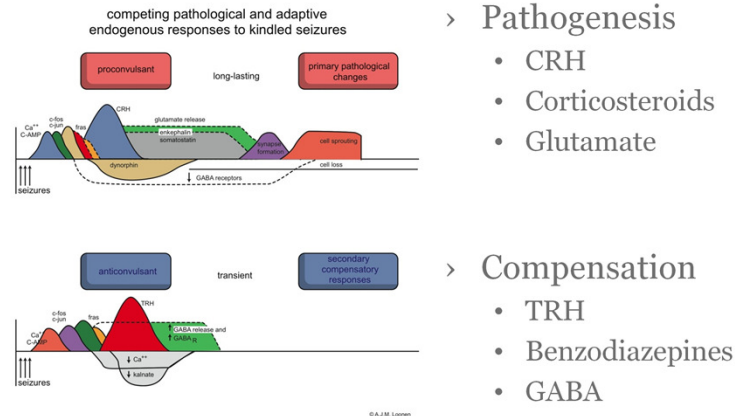
### > Spontaneous

- Generalized motor seizures
- Status epilepticus

Kindling is an electrophysiological phenomenon that occurs in the pharmacological laboratory when cortical areas of animals are daily stimulated with weak electrical stimuli. These stimuli are usually applied for 1 second per day to limbic areas such as the amygdala or the hippocampus and are subliminal which means that they are below the threshold to induce a response. However, when applied on a daily basis to the same area, they are able to activate the cortex. This first starts to result in the occurrence of after-discharges that gradually increase in duration and complexity and start to spread around through the cortical surroundings. If this stimulation is continued, full-blown motor seizures start to occur and thereafter also start to occur spontaneously in the absence of exogenous electrical stimulation.

The kindling model is used both in studies on the development of some kind of clinical seizure disorders (e.g. temporal lobe epilepsy) and on the genesis of certain behavioral disorders (particularly bipolar mood disorders). We think a similar phenomenon occurs in the affective disorder where initial episodes are triggered by psychosocial stressors, but, with enough repetition, they also begin to emerge spontaneously.

## Biochemical basis of kindling



Amygdala-kindling is accompanied by several biochemical changes involving classical neurotransmitters, neuropeptides, cytokines and neurotrophic factors. Some of these changes are believed to represent the pathophysiological process that is at the basis of the evolution of seizures. These are shown on a time axis in the upper figure of this slide. Others alterations are thought to reflect adaptative and compensatory changes that result in a transient anticonvulsant effect. These are shown in the lower figure. These last changes consist of an induction or increased expression of thyrotropin-releasing hormone (TRH), cholecystikinin (CCK), neuropeptide Y (NPY) and Benzodiazepine/GABA receptors.

A key finding, which possibly links kindling with the neuro-endocrine hypothesis, is the observation that the expression of corticotropin-releasing hormone (CRH) plays an important role in the evolution of kindled seizures. As we have seen, CRH is an excitatory transmitter that operates as the cardinal central nervous system transducer of stressful stimuli. Neurons that synthesize CRH or possess CRH receptors are abundantly present in the amygdala and hippocampus. Repeated stimulation of these receptors is known to result in limbic seizures. Moreover, corticosteroids are known to facilitate epileptic convulsions induced by electrical amygdala kindling. So, both neuronal (CRH) and humeral (steroid) factors link the endocrine HPA system to facilitation of kindling of the amygdala induced by repeated and similar stress stimuli.



## Complex influence on kindling vulnerability

- › Cytokines
  - Interleukin-6 (IL-6)
  - Tumor necrosis factor-alpha (TNF- $\alpha$ )
  - Interleukin-1 beta (IL-1 $\beta$ )
- › Neurotrophic factors
  - Brain derived neurotrophic factor (BDNF)
  - Neurotrophin-3 (NT-3)
  - Neurotrophin-4/5 (NT-4/5)
  - Neurotrophin-6 (NT-6)

Difficult to understand, but therefore perhaps even more intriguing, is the influence of cytokines and neurotrophic factors on the kindling process. (And then, let us not even not consider the complex interactions among them). Their effects are often found to be biphasic and/or very complex in nature. This is true for the most studied cytokines (IL-6, TNF- $\alpha$ , and IL-1 $\beta$ ) as well as, for example, for brain derived neurotrophic factor (BDNF). IL-6, for example, increases the vulnerability to excitotoxicity by glutamate (causing cell death), but is also involved in neuroprotection against cell death. The same is true for TNF- $\alpha$  and IL-1 $\beta$ . Also BDNF increases neuronal excitability and at the same time seems to have neuroprotective effects.

BDNF is a very important neurotrophic factor which probably plays an important role in both the genetic and environmentally induced vulnerability to the development of a (bipolar) mood disorder. Insufficient protection from the kindling phenomena by a fall of BDNF is believed to induce the development of an affective episode. The serotonergic system interacts with brain-derived neurotrophic factor (BDNF). This may explain why selective serotonin reuptake inhibitors increase the signaling of BDNF. This may be the pharmacological basis for the prophylactic activity of SSRIs in preventing recurrences of a depressive episode.



## Kindling hypothesis

- › Factors that increase the vulnerability for kindling
  - CRH and corticosteroids
  - Cytokines (IL-6, TNF- $\alpha$ , IL-1 $\beta$ )
- › Factors that decrease the vulnerability for kindling
  - BDNF
- › Uncoordinated electrical activity
- › Dysfunction of amygdala and hippocampus
- › Initiation of emotional response

Let us return to the kindling hypothesis. A few findings link this kindling hypothesis to our ideas about the pathogenesis of depression. Both corticosteroids and CRH are known to enhance the excitability of cortical neurons of the basolateral amygdala. This results in a lowering of the stimulation threshold of this cortical structure. So, repeated and malicious activation of the HPA axis may be able to induce uncoordinated electrical activity within the limbic cortex, which will finally result in hyperactivity of the limbic cortico-ganglio-thalamo-cortical circuit. The vulnerability for kindling of the amygdala is decreased by BDNF. The opposite may be true for other neurotrophic factors and cytokines. So repeated stress reactions may induce hypersensitivity to activate emotional fear/flight reactions .

Although hard evidence supporting this hypothesis is lacking, the kindling theory certainly offers one of the best explanations for illness progression in affective disease. However, it does not explain why some persons develop an affective illness and others not. Repeatedly occurring psychosocial stressful events are considered to be an ordinary aspect of life. In a normal situation, the organism is supposed to be well capable of adequately dealing with these repeated stressors. So, in depressed patients an increased vulnerability should exist. In some cases this will be an intrusive life event, like for example sexual abuse. In other cases the genetic makeup of the individual can be held responsible. And perhaps in most cases it is just related to our current unhealthy life style; lonely, loveless and living in a hostile, inhuman society.



## Expansion of kindling hypothesis

- › Increased vulnerability of amygdala for kindling
  - Genetic predisposition
  - Increased influence of stressors
- › Uncoordinated activity of amygdala
  - Exaggerated response
  - Spontaneous activity
- › Eliciting inappropriate emotional responses
- › Anti-kindling effects
  - ECT
  - Anticonvulsants
- › Pro-kindling effects
  - Amitriptyline
  - Imipramine
  - Maprotiline
- › No influence
  - Paroxetine

As a consequence of the kindling hypothesis, one would expect that biological measures which have an anticonvulsant effect on the amygdala, also have a therapeutic effect in mood disorders. And this appears to be true, at least in case of, for example, electroconvulsive therapy (ECT). ECT is believed to exert its therapeutic action on the basis of a potent anticonvulsant activity. Treatment with ECT extensively raises the convulsive threshold. It can be postulated that this anticonvulsant activity is also exhibited within the basolateral amygdala. This would then result in a reversal of the increased excitability of this limbic structure.

However, not all anti-kindling treatments result in antidepressant effects. Several anticonvulsant drugs for example are primarily active in mania. Their efficacy in the treatment of a 'bipolar' as well as a 'unipolar' depression is at the best doubtful. Only electroconvulsive therapy (ECT) appears to be effective during the treatment of both depression and mania. Moreover, several effective tricyclic antidepressant drugs have the opposite effect; they enhance the vulnerability of the amygdala to kindling. This may correspond with their potential to induce mania and 'rapid cycling' in bipolar disorder, but is not in line with their therapeutic effects in depression. It supports the hypothesis that tricyclic antidepressant drugs elicit their therapeutic effects in structures other than the hippocampal/amygdala complex. This brings into question whether or not ECT elicits antidepressant activity in this brain structure. Its effects on the hippocampus/amygdala maybe primarily related to its antimanic activity, while its antidepressive effects are found elsewhere.



## Conclusion

- › Hypothalamus
  - Norepinephrine
  - Activation by amygdala
- › Amygdala/hippocampus
  - Serotonin (5-HT<sub>1a</sub>)
  - Biorhythm (HPA axis)
  - Corticosteroids (HPA axis) → dysfunction, hypoplasia
  - Cytokines (HPA axis) → dysfunction, hypoplasia
  - Neurotrophic factors → increased excitability
- › Prefrontal cortex
  - Dopamine (D<sub>1</sub>)
  - Serotonin (5-HT<sub>2</sub>)

In summary, three sites of action may be proposed for various antidepressant treatments, and these structures may play an essential role in the pathogenesis of depressive disorders. These structures are the hypothalamus, the amygdala/hippocampal complex, and the prefrontal cortex.

The hypothalamus is directly activated by tricyclic antidepressants, which all have a certain adrenergic activity. The hypothalamus is activated by the amygdala and this structure may play a dominant role in the induction of mood disorders. Several antidepressive treatments influence the amygdala, either directly or by enhancing its inhibition. In this last process the function of the hippocampus plays a crucial role.

The prefrontal cortex is essential for response selection and motivation to reward bringing behavior. It is directly influenced by dopaminergic drugs, but more often addressed indirectly by antidepressant drugs.





## Depression may originate from two different brain structures

- › ***Brainstem/hypothalamus/prefrontal cortex***
  - Depression as a '*lust*' disorder
  - Hypoactivity of the extrapyramidal CSTC circuit
  - Anhedonia and loss of energy
- › ***Hippocampus/amygdala***
  - Depression as a '*concern*' disorder
  - Hyperactivity of the limbic CGTC circuit
  - Dysphoria and hopelessness

This brings us back to our original model. Two interacting sites can be identified from where the depressive disorder can be thought to originate:

Firstly, depression can be considered to originate from the brain stem, hypothalamus and primarily the prefrontal part of the cerebral cortex. These structures regulate the autonomic, endocrine and motivational life functions. These structures may cause the lack of energy, the lack of motivation, and also lack of pleasure that bothers the depressed patient.

Secondly, depressive symptoms can be thought to originate from the amygdala and hippocampal complex. These brain structures regulate our reactions to past and present events that endanger us from the outer world. They can be considered to cause the negative expectations, the feelings of hopelessness, and also the lack of happiness that characterize depression. Depression is also a disorder that troubles its sufferer with inappropriate concern.

Thank you very much.

Siberia, May 2013.